UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/542,499	07/15/2005	Mamoru Kobayashi	Q89144	5259

23373 7590 06/04/2008

SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
ZAREK, PAUL E	

ART UNIT	PAPER NUMBER
4161	

MAIL DATE	DELIVERY MODE
06/04/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,499	KOBAYASHI ET AL.	
	Examiner	Art Unit	
	PAUL ZAREK	4161	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-6 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-6 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date 07/15/2005.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 1-4 were amended by Applicant in correspondence on 07/15/2005. Claims 1-6 are currently pending. This is the first Office Action on the merits of the claim(s).

Priority

2. Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Japan on 01/22/2003.

Claim Rejections - 35 USC § 112 (1st Paragraph)

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 1-6 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating hyperlipidemia associated with gestational toxicosis (preeclampsia) with Formula I or Ia in rats, does not reasonably provide enablement for preventing hyperlipidemia or IUGR associated with gestational toxicosis with Formula I or Ia in rats, or preventing or treating IUGR or hyperlipidemia associated with gestational toxicosis with Formula I or Ia in any subject other than rat. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

5. *In re Wands*, 858 F.2d at 736-40, 8 USPQ2d at 1403-07, set forth eight factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." (MPEP § 2164.01(a))

A. *The breadth of the claim*: Claims 1-6 are drawn to an agent comprising a specific phenylethanolaminotetralin derivative (Formula I or Ia), a β_2-adrenergic receptor agonist, to prevent or treat intrauterine growth retardation (IUGR) or gestational toxicosis (also known as preeclampsia);

B. *Nature of the invention*: the agent is specifically drawn for the treatment or prevention of IUGR or gestational toxicosis;

C. *The state of the prior art*: Prior art teaches that the claimed phenylethanolaminotetralin derivative, Formula I or Ia (termed KUR-1246), is a highly specific β_2-adrenergic receptor agonist with enhanced potency over established β_2-adrenergic receptor agonists, ritodrine and terbutaline (Kobayashi, et al., 2001, Figure 2). KUR-1246 is an efficacious tocolytic agent (Sakakibara, et al., 2002, abstract), which is expected since other β_2-adrenergic receptor agonists (i.e. ritodrine and terbutaline) have been utilized as tocolytic agents. The Examiner found no prior art teaching the treatment or prevention of IUGR or gestational toxicosis (preeclampsia) with β_2-adrenergic receptor agonists.

IUGR and asymmetric IUGR are commonly known in the field of obstetrics. Possible causes of IUGR are diverse and not necessarily correlated (Peleg, et al, 1998, Table 1). Possible causes include placental insufficiency (i.e. preeclampsia), genetic

disorders (i.e. trisomy 21), and substance abuse. Treatment of IUGR includes treating the maternal disease, cessation of substance abuse, good nutrition, and bed rest. Treatments of IUGR do not begin until after IUGR has been diagnosed. The Examiner has found no prior art teaching the prevention of IUGR which are independent of treating an existing maternal disease or condition that may cause IUGR.

IUGR is a common but not necessary complication of preeclampsia. (von Versen-Hoeynck and Powers, 2007, pg 5462, final paragraph). Common laboratory models of preeclampsia include infusing pregnant rats with the nitric oxide synthase inhibitor, N^G-nitro-L-arginine methyl ester (L-NAME). NO inhibition leads to an increase in iNOS and induces IUGR and preeclampsia in rodents, indicating that preeclampsia may be a state of NO deficiency. However, there is disagreement whether such is the case in humans. "To date, several groups of investigators have measured the circulating or urinary levels of NO metabolites (nitrites and nitrates) and cGMP in women with pre-eclampsia, considering it to be a reflection of the activity of the NO system. However, the results are contradictory and somewhat confusing." (Buhimschi, et al., 1998, pg 31, 2nd column, 2nd paragraph) Results achieved in rats do not correlate in humans in a predictable fashion. This casts doubt whether results achieved in rats are useful predictors of treatments in any other animal;

D. *Level of one of ordinary skill in the art*: One of ordinary skill would be scientists and physicians who are trained in pregnancy, complications thereof, and treatments of pregnancy disorders;

E. *Level of predictability in the art*: Buhimschi, et al., teach the controversy of the relevance of rat models of IUGR and preeclampsia to the treatment of humans. Translating rat treatment models to another animal, especially humans, would be highly unpredictable;

F. *Amount of direction provided by the inventor*: The Specification discloses no mechanism of action concerning how Formula I or Ia specifically, or β_2-adrenergic receptor agonists in general, treat or prevent IUGR or gestational toxicosis. The Applicant states, ". . . there is no drug with established efficacy in treatment of IUGR and gestational toxicosis . . .." (pg 2, lines 13-15) The Applicant further states ". . . there has been no report on effects of [Formula I or Ia] on fetal weight loss, static gangrene in the tip of fetal extremities, and elevation of maternal urinary protein and plasma triglyceride level in IUGR and gestational toxicosis. It is completely unknown that the compounds are useful as agents for the prevention or treatment of IUGR or gestational toxicosis." A search of the current art (since 2004) offers no indication that a β_2-adrenergic receptor agonist, let alone Formula I or Ia, would be effective for the prevention or treatment for IUGR or gestational toxicosis (preeclampsia);

G. *Existence of working examples*: The Specification discloses a gestational toxicosis treatment model in which pregnant rats are given L-NAME and then treated with saline or Formula Ia. The disclosure shows results indicating that fetuses in dams treated with Formula Ia have an increase body weight and decreased number of static gangrene in the tip of extremities compared to control group. (Tables 1 and 3). Tables 4

and 5 demonstrate that treatment with Formula Ia in pregnant rats with IUGR have lower urinary albumin and plasma triglyceride levels than the control group.

Examiner notes that the Applicant did not indicate that the increase in fetal body weight (Table 1) between the test and control groups was statistically significant. Stedman's Medical Dictionary, 27th Ed., defines statistics as a "collection of numerical values, items of information, or other facts which are numerically grouped into definite classes and subject to analysis, particularly analysis of the probability that the resulting empirical findings are due to chance." Absent an indication demonstrating statistical significance, the Examiner asserts that the increase in body weight is not necessarily a result of treating the pregnant mother with Formula Ia.

The Specification discloses no working examples of preventing IUGR in rats with Formula I or Ia.

The Specification discloses no working examples of preventing or treating IUGR in humans with Formula I or Ia.

The Specification discloses no working examples of preventing or treating gestational toxicosis in humans with Formula I or Ia; and,

H. *Quantity or experimentation needed to make or use the invention based on the content of the disclosure*: Claims 1-6 are directed to the prevention or treatment of IUGR or gestational toxicosis. The Specification has not disclosed how Formula I or Ia prevents or treats IUGR and gestational toxicosis (preeclampsia). Moreover, the Specification is silent as to how an effective treatment in rats would translate into an effective treatment in humans. In view of Buhismchi, et al., a skilled artisan would have

no direction in translating the treatment for IUGR and gestational toxicosis with Formula I or Ia disclosed in the Specification to any animal other than a rat.

The Specification is also silent with respect to preventing IUGR or gestational toxicosis. No potential patient population is disclosed, nor is any example given demonstrating the efficacy of Formula I or Ia in preventing IUGR or gestational toxicosis. The Examiner is not aware of any regimen by which IUGR or gestational toxicosis is prevented. Undue experimentation would be required to use the invention as claimed.

Claim Rejections - 35 USC § 102

6. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

7. Claims 1-6 are rejected under 35 U.S.C. 102(b) as being anticipated by Yanagi, et al, (Chem. Pharm. Bull, 2001).

8. Claims 1, 3, and 4 of the instant application claim a phenylethanolaminotetralin derivative (Formula I). Yanagi, et al., teach the exact compound in Chart 7, Compound 28.

9. Claims 2, 5, and 6 of the instant application claim the phenylethanolaminotetralin derivative in a salt formulation (Formula Ia). Yanagi, et al., teach the exact compound in Figure 1. Thus, Yanagi, et al., read on all the limitations of Claims 1-6 of the instant application because it they teach both Formulae I and Ia.

10. The preambles of Claims 1-6 specify an intended use for Formulae I and Ia. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

Conclusion

11. No claims are allowed.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL ZAREK whose telephone number is 571-270-5754. The examiner can normally be reached on Monday-Thursday, 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, PATRICK NOLAN can be reached on 571-272-0847. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

PEZ

/Patrick J. Nolan/

Supervisory Patent Examiner, Art Unit 4161